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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,947	06/06/2006	Bertrand Leblond	BJS-3665-181	5513

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EXAMINER	
BROOKS, CLINTON A	

ART UNIT	PAPER NUMBER
1621	

MAIL DATE	DELIVERY MODE
05/07/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,947	LEBLOND ET AL.	
	Examiner	Art Unit	
	CLINTON BROOKS	1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/1/2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-41* is/are pending in the application.

4a) Of the above claim(s) *23-26,28,34 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22, 27, 29-33, 36-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is **FINAL**.

Status of Claims

Claims 22-41 are currently pending. Independent claims 22, 37, 38, 39, 41 stand currently amended. In view of amendment, the new art of record reading on claims 22,27, 29-33, 36-41, and therefore claims 23-26, 28, and 34-35 are withdrawn from consideration pursuant to Markush practice as not being anticipated by the art below.

Claim Rejections – 35 USC § 112/First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

. **Claims 37-41, stand** rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds EHT9299, EHY7706, EHT7800, and EHT3741, does not reasonably provide enablement for the use claims, which claim the use of the millions of compounds disclosed in the genus of formula I as HDAC inhibitors, treatment of central and peripheral nervous systems diseases or neurodegenerative diseases, treatment of fibrosis, cancer, or reducing cancer cell proliferation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The Nature of the Invention

Claims 37-41 relate to a method for treatment of conditions mediated by HDAC such as cancer, psoriasis; treatment of central and peripheral nervous system diseases or neurodegenerative diseases; treatment of fibrosis; a variety of cancer types; and reducing cancer cell proliferation in all can cell lines.

The State of the Prior Art and the Predictability or lack thereof in the art

With respect to the state of the prior art the instant specification cites scientific articles and pending patent application that according to Applicants disclose:

1. That it is known that HDACS can catalyze the removing of the acetyl group from lysine residues in the N-terminus tails of nucleosomal core histones resulting in a more compact chromatin structure that is associated with repression of transcription.

2. That HDACs are involved in cell-cycle progression and differentiation; that the specific compounds--trichostatin A and SAHA are effective in a mice promyelocytic leukemia model.

3. Trichostatin A has been used in the treatment of fibrosis.

4. SAHA improves the motor impairment in R6/2 mice (a Huntington's disease model).

5. That HDAC inhibitors could be useful for treating diseases of the central nervous system in particular neurodegenerative diseases such as polyglutamine expansion diseases.

Further, the instant specification discloses that 9 human HDACs have been characterized and that two are inferred. Further, the instant specification discloses that two classes of HDACs

are relevant because they are not NAD-dependent enzymes (Class I: HDAC 1,2,3,8; Class II, 4-6, and 7-10). Further, the instant disclosure states that SAHA inhibits both classes.

With respect to the lack of predictability in the art, the diseases recited in the instant claims represent a group with diverse etiologies. Further, there are many isoforms of the HDAC enzyme which are located in different locations within a cell--some in the nucleus and some in the nucleus and cytoplasm (instant specification page 2). As stated in the instant specification, different HDACs may be causative for different diseases.

Further, the instant specification discloses that active experimentation is ongoing stating that "[a] very few of small molecules are known that selectively target either of the two classes (class 1 or class 2) or individual members (HDAC 1-10) of the family) (page 2 of specification).

The combination of all these factors point to an early stage in the state of the art and a lack of predictability in the art.

The amount of direction or guidance present and the presence or absence of working examples

The specification discusses at page 64 that an HDAC activity assay was performed and that IC50 for 4 compounds were disclosed EHT9299, EHT7706, EHT7800, and EHT3741. Applicants' argue that these results illustrate the ability of the efficiency of the compounds of this invention to affect specifically HDAC enzymatic activity. No animal model for any disease model are presented. No data for an HDAC profile (all the HDAC enzymes or a cell line panel) against SAHA or trichostatin A that would suggest similar results based on similar HDAC inhibition is presented. Millions if not billions of compounds are presented.

The breadth of the claims

The claim is extremely broad in that it is drawn to the use of any compound of generic formula (I) for the treatment of any type of cancer, or other diseases as stated above.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the inventions is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compound exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of the instant claims for the treatment of cancer and the other diseases recited, as a result necessitating one of skill to perform an exhaustive search for which compounds of the instant claims will be useful, if any, in order to practice the claimed invention.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what compounds, if any, out of all compounds, would be effective in treating cancer and the other diseases

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instantly claimed methods. In view of the breadth of the claim, the chemical nature of the invention, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill

in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which compositions would treat cancer, psoriasis, central and peripheral nervous system diseases or neourodegenerative diseases, fibrosis, cancer cell proliferation in all cell lines with no assurance of success.

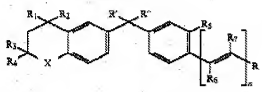
Claim Rejections – 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

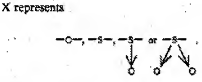
Claims 22,27, 29-33, 36-41 are rejected under 35 U.S.C. 102(b) as being anticipated by United States Patent No. 4829080 ("the '080 patent").

The '080 patent teaches at least the genus:



(I)

wherein,
n is 0 or 1,
X represents



R' represents hydrogen, OH, alkoxy having 1–4 carbon atoms, acyloxy having 1–4 carbon atoms, or NH_2,
R'' represents hydrogen, or alkoxy having 1–4 carbon atoms,
or R' and R'' together form an oxo radical (=O), a methano radical (=CH_2) or a hydroxyimino radical (=N—OH),
R represents —CH_2OH or —COR_8,
R_8 represents hydrogen,

R_9 represents hydrogen, linear or branched alkyl having 1-20 carbon atoms, mono or polyhydroxyalkyl, aryl or aralkyl optionally substituted, or the residue of a sugar or even the radical

at column 1.

Further, the '080 patent teaches at least the following amide specie (col. 19):

EXAMPLE XIX

Preparation of N-ethyl 6-(4,4-dimethyl-3,4-dihydro-6-benzopyranyl) carbonyl-2-naphthalene carboxamide.

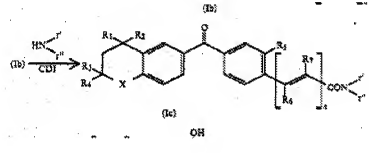
Compound of formula III wherein X=—O—, $R_1=R_2=CH_3$, $R_3=R_4=H$, R' andR''=oxo and R_5=NHet.

A suspension of 1.98 g (5.5 mmoles) of 6-(4,4-dimethyl-3,4-dihydro-6-benzopyranyl) carbonyl 2-naphthalene carboxylic acid and 1.07 g (6.6 mmoles) of N,N'-carbonyl diimidazole in 50 cm^3 of anhydrous dichloromethane is stirred for 1 hour at ambient temperature. There is then added 0.5 cm^3 (7.15 mmoles) of anhydrous ethylamine to the resulting solution and the solution is stirred for 3 hours at ambient temperature. The reaction mixture is diluted with 30 cm^3 of dichloromethane, then washed successively with 25 cm^3 of N HCl and then 3 times with 25 cm^3 of water. The dichloromethane phase is dried on sodium sulfate and evaporated to dryness under reduced pressure. The crude amide is purified by silica 60 gel chromatography using an eluant mixture of 2/8/90 acetic acid/dioxane/toluene followed by recrystallization in a mixture of isopropylether/acetone. After drying, 1.1 g of N-ethyl 6-(4,4-dimethyl-3,4-dihydro-6-benzopyranyl) carbonyl-2-naphthalene carboxamide in the form of a white solid having a melting point of 174° C. are obtained.

The NMR ^1H spectrum 250 MHz conforms to the expected structure.

Elemental analysis: $C_{23}H_{25}NO_3$ Calculated: C: 77.49 H: 6.50 N: 3.61 O: 12.39 Found: 77.31; 6.55; 3.70; 12.67.

Further, the '080 patent teaches the following subgenus at col. 5 and 6):



Further, the '080 patent teaches utility in pharmaceutical and cosmetic compositions (at least abstract) and dermatological diseases. Further, the '080 patent teaches that these compounds are useful in kerantinization disorder (differentiation-proliferation)) and dermatological diseases (or others) having inflammatory and/or immunoallergic components and in the treatment of illnesses of the degeneration of cognitive tissue. Further, the '080 patent

teaches that these compounds exhibit anti-tumor activity. For example the '080 patent teaches (col. 1):

BACKGROUND OF THE INVENTION

The present invention relates to new aromatic benzopyranyl and benzothiopyranyl compounds, to a process for their preparation and to their use in human or veterinary medicine and in cosmetic compositions.

These new compounds are usefully employed in the topical and systemic treatment of dermatologic diseases linked to a keratinization disorder (differentiation—proliferation) and dermatologic diseases (or others) having inflammatory and/or immunoallergic components and in the treatment of illnesses of the degeneration of conjunctive tissue. They also exhibit anti-tumor activity.

Moreover, these compounds can be employed in the treatment of atrophy, be it cutaneous or respiratory, and in the treatment of rheumatoid psoriasis.

These compounds also possess good activity against the germs involved in acne.

Finally, the compounds of the present invention are usefully employed in the opthamology field and principally in the treatment of corneopathies.

Response to Applicants' Arguments/Amendments

In view of Applicants' amendment the claim objection to claim 22 is withdrawn.

In view of Applicant's amendment the 112/Second paragraph rejection regarding the term "preferably" in claim 22 is withdrawn.

In view of Applicants' amendment the 112/ Second paragraph rejection regarding "their salts" is withdrawn.

In view of Applicants' amendment the 112/Second Paragraph rejection regarding "or an ester derivative" is withdrawn.

In view of Applicants' amendment the 112/ Second Paragraph rejection regarding "the groups identified in claim 1" is withdrawn.

In view of Applicants' amendment the 112/First Paragraph rejection regarding "hydrates or mixtures containing hydrates" is withdrawn.

In view of Applicants' amendment the 102 and 103 rejections is view of 5567721 ("the '721 patent") are withdrawn.

In view of Applicants' amendment and withdrawn rejections above the arguments relating to such rejections are moot.

With respect to the 112 first paragraph rejection that is maintained above, Applicants' amendment/arguments have been considered but are not found to be persuasive for at least the following reasons. The amendment places the method of treating claims dependent from the 11 species recited in claim 34.

As stated in the rejection, the claims are drawn to a variety of diseases, and the only data provided in the specification is the inhibition of EHT 9299, EHT 7706, EHT 7800, and EHT 3741. Further, the data is provided and compared to TSA and SAHA. The question of causality remains. In Applicants disclosure, they state that [n]ine HDACs have been characterized and two inferred" (page 2). Applicants cite studies of Tricostatin A that have been reported to be useful in the treatment of fibrosis. In addition, Applicants cite the data from studies with SAHA and argue "certain" HDAC inhibitors can cross the blood brain barrier to inhibit HDAC activity causing the accumulation of acetylated histones in the brain (page 2 of disclosure). Applicants are comparing TSA and SAHA to the four compounds above. However, there is no profile with respect to the 9 different HDACS and whether or not one skilled in the art based on a similar HDAC profile would expect a similar result as that of TSA or SAHA. There are no studies provided that shows these compounds are effective in the animal models cited. Further, there is

no data on blood brain barrier penetration of these compounds. Without additional data, the amount of experiment required is deemed undue.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CLINTON BROOKS whose telephone number is (571)270-7682. The examiner can normally be reached on Monday-Friday 8:00 AM to 5:00 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, DANIEL SULLIVAN can be reached on (571)272-0779. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about

the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Cab

/Daniel M Sullivan/
Supervisory Patent Examiner, Art Unit 1621